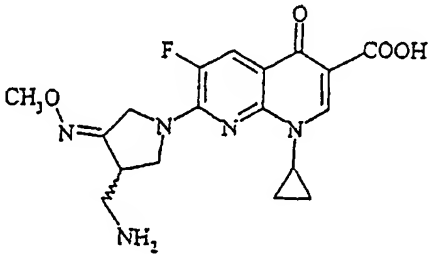




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP99/07003 (22) International Filing Date: 15 September 1999 (15.09.99) (30) Priority Data: 9820405.0 18 September 1998 (18.09.98) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HAYES, Jerome, Francis [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). WALSGROVE, Timothy, Charles [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). WELLS, Andrew, Stephen [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). (74) Agent: BLAKEY, Alison, Jane; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE (METHANESULFONATE SESQUIHYDRATE) <div style="text-align: center;">  <p>(I)</p> </div> (57) Abstract <p>The present invention relates to an improved process for the production of the methanesulfonate sesquihydrate which comprises direct salt and hydrate formation. According to the invention there is provided a process for the production of 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises reacting 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of formula (I) having antibacterial activity and methanesulfonic acid in a solvent comprising at least one water miscible cosolvent and water, and isolating the resulting solid product.</p>		

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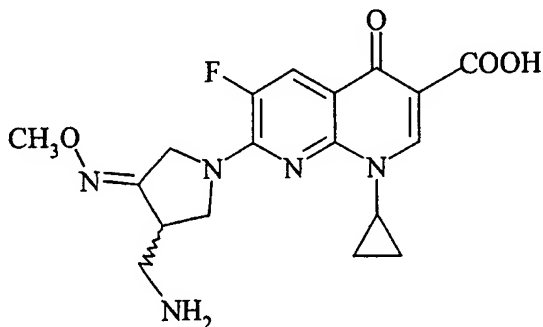
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PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE (METHANESULFONATE SESQUIHYDRATE)

The present invention relates to a process for the production of a naphthyridine carboxylic acid derivative having antibacterial activity.

5 EP 688772 discloses novel naphthyridine carboxylic acid derivatives, including anhydrous (R,S)-7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of formula I, having antibacterial activity.



I

10 WO 98/42705 (published after the priority date of the present application) discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate (the "methanesulfonate sesquihydrate").

15 WO 98/42705 discloses a process for the production of the methanesulfonate sesquihydrate comprising reaction of the corresponding free base with methanesulfonic acid in dichloromethane / ethanol followed by recrystallisation of the resulting crude salt anhydrate from either water : acetone (10:7 v/v), or water : ethanol (1:2 v/v). The overall yield for this two step process is 70-80%. An alternative process for the production of the

20 methanesulfonate sesquihydrate described in WO 98/42705 comprises exposing a solvate of the methanesulfonate (ethanol 0.11%) to high relative humidity (nitrogen >93% humidity).

The present invention relates to an improved process for the production of the methanesulfonate sesquihydrate which comprises direct salt and hydrate formation.

25 According to the invention there is provided a process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises reacting 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and

30 methanesulfonic acid in a solvent comprising at least one water miscible cosolvent and water, and isolating the resulting solid product.

The 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (hereinafter referred to as "the free base") used in the process of the invention may be prepared as described in EP 688772.

5 Water miscible cosolvents which may be used in the process of the invention include C₁₋₈ alcohols, acetonitrile and dimethylformamide. The water miscible cosolvent is preferably a C₁₋₄ alcohol or a mixture thereof, e.g. methanol, ethanol and propanol; the preferred C₁₋₄ alcohol is isopropanol.

10 In addition to at least one water miscible cosolvent and water the solvent may contain other components, such as C₁₋₄ haloalkanes. However, the solvent preferably comprises essentially of a water miscible cosolvent and water.

Suitable ratios of water miscible cosolvent : water for use in the process of the invention include ratios in the range 10:1 to 1:2 v/v, preferred ratios are in the range 10:1 to 1:1 v/v, more preferably a ratio of water miscible cosolvent : water of 2:1 v/v is used.

15 Any suitable ratio of free base to solvent may be used, for example, a ratio of up to 1:100 w/v, particularly a ratio of about 1:9 w/v.

The process of the invention may suitably use from 0.7 to >3 mole equivalents of methanesulfonic acid, preferably 0.7 to 1.5 equivalents, more preferably 0.9 to 1.5 equivalents, especially about 1.0 equivalent of methanesulfonic acid (based on the free
20 base).

The mixture of the free base and methanesulfonic acid may be warmed in the solvent to aid dissolution. On cooling the methanesulfonate sesquihydrate will crystallise out of solution. To aid crystallisation the solution may be seeded with a small quantity of solid methanesulfonate sesquihydrate. In order to obtain polymorphically pure
25 methanesulfonate sesquihydrate it is preferable that seeding of the solution is completed before crystallisation begins. Seeding of the crystallisation solution is preferably performed at a temperature $\geq 25^{\circ}\text{C}$, for example at a temperature of about 30°C .

The process of the invention may be used to produce racemic methanesulfonate sesquihydrate or may be used for the production of enantiomerically enriched or
30 enantiomerically pure methanesulfonate sesquihydrate, using racemic or enantiomerically enriched or enantiomerically pure free base. Enantiomerically enriched or enantiomerically pure free base may be prepared by resolution of the racemic free base, e.g. by chiral HPLC.

The process according to the invention has the advantage that direct salt formation eliminates one step in the synthesis and gives a high yield of high purity methanesulfonate
35 sesquihydrate. In turn these advantages result in improved throughput and savings in labour and materials costs during manufacture.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication

were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following example. However, it should be understood that the example is intended to illustrate but not in any manner limit the scope of the invention.

Example 1 : Preparation of the methanesulfonate sesquihydrate

To a suspension of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (20.00 g, 51.4 mmol) in isopropanol (120 ml) and water (60 ml) was added methanesulfonic acid (3.300 ml, 50.9 mmol) at 38-40°C. The resultant dark brown solution was stirred for 15 min after which time charcoal (6.00 g of Darco G-60) was added. The suspension was stirred at 38-40°C for 4h then filtered. The filtrate was allowed to cool to 30°C and seed crystals of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate (15 mg) added. A precipitate began to form within 15 min. The suspension was allowed to cool to 20-23°C over 90 min and was stirred for 36h. The slurry was cooled to 0-5°C for 60 min then filtered and washed with isopropanol (50 ml and 44 ml). The product was sucked dry for 30 min and then further dried at 50-55°C under vacuum. The dried product was exposed to the atmosphere for 18h to give the methanesulfonate sesquihydrate 21.29 g (85%), purity >99.5% by HPLC.

The X-ray diffraction pattern of the methanesulfonate sesquihydrate was measured as follows:

	Diffraction type:	PW1710 BASED
25	Tube anode:	Cu
	Generator tension [kV]:	40
	Generator current [mA]:	30
	Wavelength Alpha1 [Å]:	1.54060
	Wavelength Alpha2 [Å]:	1.54439
30	Intensity ratio (alpha1/alpha2):	0.500
	Divergence slit:	AUTOMATIC
	Irradiated length [mm]:	12
	Receiving slit:	0.1
	Spinner:	ON
35	Monochromator used:	YES
	Start angle [°2θ]:	3.500
	End angle [°2θ]:	35.000
	Step size [°2θ]:	0.020

	Maximum intensity:	2970.250
	Time per step [s]:	2.300
	Type of scan:	STEP
	Minimum peak tip width:	0.10
5	Maximum peak tip width:	1.00
	Peak base width:	2.00
	Minimum significance:	0.50

The X-ray diffraction pattern of the methanesulfonate sesquihydrate is shown in Figure 1. The compound shows characteristic peaks at $2\theta = 8.2, 12.2$ and 14.6° .

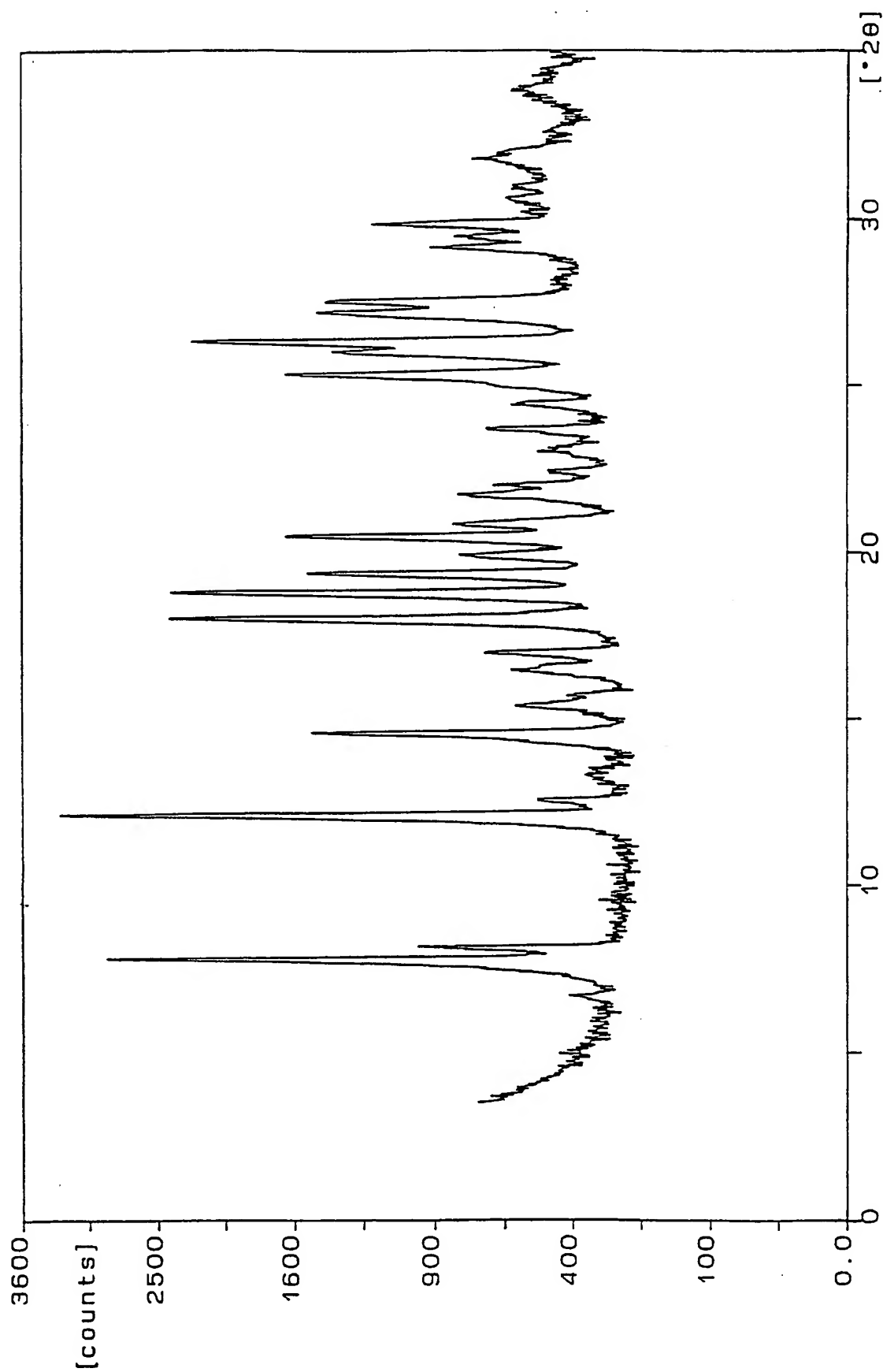
10

CLAIMS

1. A process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises
5 reacting 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in a solvent comprising at least one water miscible cosolvent and water, and isolating the resulting solid product.
- 10 2. A process according to claim 1 wherein the water miscible cosolvent is a C₁₋₄ alcohol.
3. A process according to claim 2 wherein the water miscible cosolvent is
15 isopropanol.
4. A process according to any one of the preceding claims wherein the ratio of water miscible cosolvent : water is in the range 10:1 to 1:2 v/v.
- 20 5. A process according to claim 4 wherein the ratio of water miscible cosolvent : water is 2:1 v/v.
6. A process according to any one of the preceding claims wherein the ratio of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is up to 1:100 w/v.
25
7. A process according to any one of the preceding claims which uses from 0.7 to mole 1.5 equivalents of methanesulfonic acid.
- 30 8. A process according to any one of the preceding claims wherein the recrystallisation solution is seeded with 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.
- 35 9. A process according to claim 8 wherein the solution is seeded whilst at a temperature of $\geq 25^{\circ}\text{C}$.
10. A process according to claim 9 wherein the solution is seeded whilst at a

temperature of about 30°C.

1/1

FIGURE I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07003

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 96 39406 A (HANDANYAN LYNNE A ; JOHNSON PHILLIP J (US); MORRIS THOMAS A (US); N) 12 December 1996 (1996-12-12) * see page 1, formula 1, and page 4, preparation A * the whole document ---	1-10
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31 January 2000

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01/03/2000

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